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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/063,978	04/21/1998	ROBERT J. OBREMSKI	45D-1750(641	5283

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	32

DATE MAILED: 08/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/063,978	OBREMSKI ET AL	
	Examiner	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 28, 2002 has been entered.

2. Claims 1-28 are pending in this office action.

Response to Arguments

3. Applicant's arguments filed May 28, 2002 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The rejection of claims 1-4, 13-19, 21 and 23-28 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) is maintained for reasons previously set forth.

Applicants argue that all three independent claims 1, 23 and 26 require: a microscopic size of the sorbent zones; a substantial depletion of analyte from the sample; and a concentration of the depleted analyte on the microscopic sorbent zones. It is agreed that the claims require a microscopic sorbent zone and substantial depletion of analyte; and the claims further state that the analyte is concentrated on the microscopic sorbent zones. However, it would have been obvious to one of skill in the art that when immobilized antibodies are used to capture analyte, the analyte captured is concentrated in said area.

The declaration and applicant argue that Figures 4 does not teach substantial depletion of an analyte because Figure 4 shows that theoretically given enough binding partner and enough time, one can bind any amount of analyte and that Figure 4 does not accurately reflect non-equilibrium and non-first order analyte binding by microscopic sorbent zones occurring in the instant invention. The figure is representative of the idea of substantial analyte depletion and teaches that substantial deplete in microsorbent zones can occur. Therefore even though figure 4 may be theoretical, the entire article teaches how to obtain substantial analyte depletion in microsorbent zones as required by the claims, i.e., by using a high concentration of antibodies. Thus, Ekins (J. of Clinical Immuno) teach that no unexpected results are achieved when using high concentrations of antibody to substantially deplete analyte in a sample since Ekins (J. of Clinical Immuno) already teaches such knowledge was known in the art.

Applicants and the declaration argue that high-density coating was not desirable because blocking of the lowers layers by the top layers substantially decreases binding. However the instant specification defines substantial depletion to be at least about 60% of analyte. Therefore, as long as the art teaches how to achieve at least 60% analyte

depletion it meets the limitations of the claims. Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach substantial analyte depletion as defined by the instant application. There is no limitation in the claim that blocking may or may not occur, but simply that the analyte be substantially depleted. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the blocking feature upon which applicant relies is not recited in the rejected claims.

Applicant argues that '202 teaches away from an increase in coating density because it states that high quantities of binding agents is neither necessary for sensitivity. However, '202 teach having 10^5 to 10^8 molecules of binding agent at each individual location, or sorbent zone. Thus '202 teach an assay wherein the amount of analyte binding partner immobilized in a sorbent zone is from 10^5 to 10^{10} molecules of analyte binding partner as claimed.

Applicant argues that the instant specification discusses irregular topology of the immobilized binding partner molecules extending up to 200nm vertically from the surface of the film, the use of photo-linking techniques and printing antibody at concentrations 1000 times greater then the 1uM solutions. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., immobilized binding partner molecules extending up to 200nm vertically from the surface of the film, the use of photo-linking techniques and printing antibody at concentrations 1000 times greater then the 1uM solutions are not recited in the rejected claims. Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants again argue that the microscopic sorbent zones unexpectedly deplete substantially all analyte from the sample and concentrate the analyte onto the small measurement region. Applicant also states that there is an unexpected benefit of high signal-to-background ratio of binding assay by concentrating the signal on the small area of support.

However, '202 teach small sample sizes in individual micro-arrays wherein the concentration of binding reagent may range from 10^5 to 10^{10} molecules of binding agent. Understanding that the recognition of such small amounts of binding agents is permissible, next it is feasible to place the binding agent required for a single concentration measurement on a very small area of a solid support. A high coating density is generally desirable to maximize signal/noise ratios. Ekins (J. of Clinical Immuno) teach measuring the analyte concentration in the medium to which the antibody is exposed wherein the analyte binding by antibody clearly causes analyte depletion in the surrounding medium. Therefore, Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach microscopic sorbent zones that substantially deplete analyte from the sample and concentrate the analyte onto the microsorbent zones. Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach using large amounts of antibody to capture analyte in a small sample, which substantially deplete the sample of analyte.

Applicant argue that the instant application teaches 10-100 times higher binding capacity of the arrays and 10-100 times higher sensitivity of the assay. No more then routine skill is involved in adjusting the amount of a component, such as the amount of binding partner of the claimed process to achieve results taught in the prior art, even if the results are better then expected. Changes in concentrations or other process conditions of an old process do not impart patentability unless the recited ranges are critical and produce new and unexpected results. The increases in binding capacity is not unexpected since the prior art teaches that given enough binding partner and time, one can bind any amount of analyte.

Applicants argue that total analyte mass us determined in the instant application. However the steps include detecting fluorescence emissions and determining mass. The prior art teach detection of fluorescent emissions. Applicants use of analyte mass appears to be identical to the prior arts reference to analyte concentration. The laser analysis of applicants analyte mass does not provide the weight of the analyte, but provides the concentration, just as the prior art references. Therefore, applicants' argument that the assays are providing different measurements is unpersuasive.

5. The rejection of claims 1-4, 13-19, 21 and 23-28 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.) is maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious at the time of applicants invention to modify the assay to use well-known techniques for determining analyte mass or concentration. One would have a reasonable expectation of success in modifying the assay since Ekins (analytica) teach the development of microspot multi-analyte immunoassays using dual fluorescent-labeled antibodies. Moreover, no more then routine skill would have been required to modify to assays when the art teaches using analyte binding using the binding partner to substantially deplete analyte in the surround medium.

Thus applicants arguments that the combination of references does not teach substantial depletion of the analyte from the sample is unpersuasive since Ekins et al., (Analytica Chimica Acta.) teach substantial depletion of analyte in the surrounding medium.

6. The rejection of claims 5-10 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) and either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), in further view of Ullman et al., (US Patent 5,512,659) is maintained. Ekins et al.(EP 304,202), Ekins et al., (J. of Clinical Immuno.) and Ekins et al., (Analytica Chimica Acta.) have been discussed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious at the time of applicants invention to have used the first binding partner, conjugate, biotin-avidin labels and biotinylated antibodies as taught by Ullman et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Ullman et al., teach that these methods are more versatile and convenient than the known methods.

7. The rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in further view of Waggoner et al., US Patent (5,368,486) is maintained for reasons of record.

Again applicants argument that there is no suggestion to combine the references and that the combination of references does not teach or suggest the instant application. It is recognized that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

However, it would have been prima facie obvious at the time of applicants invention to modify the assay to use cyanine dyes as taught by Waggoner et al., with well-known techniques for determining analyte mass or concentration. One would have

a reasonable expectation of success in modifying the assay since Waggoner et al., teach that these cyanine dyes are intrinsically more fluorescent; have improved photo stability and improved water solubility. Moreover, no more then routine skill would have been required to modify to assays when Waggoner et al., teach that these cyanine dyes can label a wide variety of biological materials and subject to a variety of excitation wavelengths using lasers. Therefore, applicants' arguments are not persuasive.

8. The rejection of claim 12 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Waggoner et al., US Patent (5,368,486) in further view of Lee et al., (US Patent 5,453,505) is maintained. In this case, applicants argue that there is no suggestion to combine the references, however the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the assay to use the most stable dye was found to be the dye with the shortest wavelength, Cy5 whose structure contains five methine groups, while the remaining dyes contain seven methine groups, such as Cy7 that has similar stability. One would have a reasonable expectation of success in modifying the assay since a Cy5 or Cy7 have a reduced tendency to aggregate. Moreover, no more then routine skill would have been required to modify to assays when Cy5 and Cy7 are known to enhance photo stability. Therefore, applicants' arguments are not persuasive.

9. The rejection of claim 20 under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Northrup et al (US Patent 5,639,423) is maintained. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

In this case it would have been prima facie obvious at the time of applicants invention to modify the assay to incorporate the use a well known method of dispensing material using a jet printer as taught by Northrup et al. One would have a reasonable expectation of success in modifying the assay because Northrup et al., teach that the dispensing method is especially advantageous for biochemical reactions. No more then routine skill would have been required to modify to assay to incorporate immobilizing reagents onto micro instruments using the modified jet printer when jet printers are used to form the array. Therefore the arguments are not persuasive.

10. The declaration John Silzel, Ph.D., under 37 CFR 1.132 filed May 28, 2002 is insufficient to overcome the rejection of claims 1-28 based upon insufficiency of disclosure. As discussed above, figure 4 may be theoretical, however the article teaches how to obtain substantial analyte depletion in microsorbent zones as required by the claims, i.e., by using a high concentration of antibodies. Furthermore, the claims of the instant application do not limit the binding process or blocking as discussed by

the declaration, thus the declaration is not commensurate in scope when compared to the instant claims. Moreover, the declaration addresses limitations that are not claimed or limited by the instant application such as: immobilizing binding partner molecules extending up to 200nm vertically from the surface of the film, the use of photo-linking techniques and printing antibody at concentrations 1000 times greater then the 1uM solutions are not recited in the rejected claims. Finally the declaration states that the results are unexpected given the complexities of nonequilibrium conditions, cooperativity in binding, diffusion, local concentration effects and other nonlinear effects occurring with sorption on microscopic sorbent zones, however many of the complexities are discussed by the prior art and fall within the ranges claimed by the instant application.

Thus, Ekins (J. of Clinical Immuno) teach that no unexpected results are achieved when using high concentrations of antibody to substantially deplete analyte in a sample since Ekins (J. of Clinical Immuno) already teach such knowledge was known in the art. Therefore, the declaration is not persuasive.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines
August 1, 2002

MARK NAVARRO
PRIMARY EXAMINER